CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Butylate

Chemical Code # 000565, Tolerance # 00232
SB 950 # 347

Original date 6/12/97
Revised date 2/27/98

I. DATA GAP STATUS

Combined, rat: (Chronic + Oncogenicity)	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, inadequate study, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	Data gap, no adverse effect indicated
Neurotoxicity:	No data gap, possible adverse effect (rat)

Toxicology one-liners are attached.

All record numbers through 134265 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T980227
Prepared by H. Green and P. Iyer, 6/12/97; P. Iyer, 2/27/98

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

017, 018, 019, 020, 021, 022, 023, 024, 025, 026, 027, 028, 029, 030, 055, 012 037016, 037017, 037018, 037019, 037020, 037021, 037022, 037023, 037024, 037025, 037026, 037027, 037028, 037029, 085224, 073368, 073369, 073370, 022833, "A Two Year Oral Toxicity/Carcinogenicity Study of R-1910 in Rats", (Carol S. Auletta, Bio/dynamics Inc., Report # T-6515, 26 April 1982). The test article is identified as Sutan Technical R-1910. 70 Charles River Sprague-Dawley CD® rats/sex/group received 0 (Purina Lab Chow®), 50, 100, 200 and 400 mg/kg/day in the diet for 24 months. Increased male and female relative liver weights are noted at 100, 200, and 400 mg/kg/day at the 12, 18, and 24 month necropsies. Chronic NOEL = 50 mg/kg/day (reduced female bodyweights at 100 (10% to 16% reduction), 200 (10% to 26% reduction), and 400 mg/kg/day (10% to 28% reduction). **Adverse effects are not indicated. Oncogenicity NOEL = 400 mg/kg/day. **Acceptable**. (H. Green and P. Iyer, 10/9/96).

CHRONIC TOXICITY, RAT

014 012 037013 022836, "56-Week Feeding Study in Rats", (Janet A. Trutter, Hazleton Laboratories America, Inc., VA., Report # T-6118, 22 September 1978). The test material is identified as Sutan Technical with 98% purity. 60 Sprague-Dawley rats per sex per group received 0, 10, 30, or 90 mg/kg/day in the diet for 56 weeks. During week 15, the dietary level for ten rats per sex from the high dose group was increased to 180 mg/kg/day. Variations are noted for hemoglobin (decreased) and mean platelet count (increased) values in females at 180 mg/kg/day. Total protein values were elevated for males at 30, 90, and 180 mg/kg/day and for 180 mg/kg/day females. Reduced bodyweight of from 2.5% to 7% is noted for both sexes at 180 mg/kg/day. **Possible adverse effect**: an increased incidence of interstitial cell hyperplasia and interstitial cell tumors of the testes is noted for 90 mg/kg/day males. Chronic NOEL = 30 mg/kg/day. **Unacceptable** and not upgradeable (dosing rationale, no ophthalmology, incomplete histopathology, study is too short). (H. Green and P. Iyer, 3/17/97).

012 023103, "A 13-Week Dietary Study in Rats with Sutan® Technical", (M. W. Woodard, Woodard Research Corporation, Herndon, VA. 2/16/67. Report # T-2052, Submitted by R. Potrepka, Stauffer Chemical Company, Farmington CT., 12/14/84. Sutan® Technical was administered in the diet to 20 rats of each sex to achieve dose levels of 0, 8, 16 or 32 mg/kg/day. Data collected were survival, general appearance, behavior, body weight, food consumption, hematology, clinical chemistry, gross pathology, organ weights and histopathology. No treatment-related adverse effects were observed. No worksheet. Subchronic study, supplemental information (P. Iyer, 4/21/97).

CHRONIC TOXICITY, DOG

**041, 062437, "A Twelve Month Oral Toxicity Study of Sutan® Technical in Dogs", (Ira W. Daly, Bio/dynamics, Inc., East Millstone, N.J., Report # T-12651, 14 September 1987). The test article is identified as Sutan® Technical. 5 Beagle dogs/sex/group received 0 (empty gelatin capsules), 5, 25, and 100 mg/kg/day by gelatin capsule 7 days per week for 52 weeks. Platelet and leukocyte counts were elevated at 3, 6, and 12 months for high dose males and females. Decreased erythrocyte count and hematocrit were noted for high dose females at 3, 6, and 12 months. Alkaline Phosphatase was increased for high dose males and females at 3, 6, and 12 months. Relative liver weights were increased for males and females at 25 and 100 mg/kg/day. Male and female relative thyroid/parathyroid weights were increased for high dose

males and females. **Adverse effects are not indicated.** Chronic NOAEL = 25 mg/kg/day (increased relative liver weights at 25 and 100 mg/kg/day). **Acceptable** (H. Green and P. Iyer, 3/19/97).

046 065968 Duplicate of 041 062437

043 062438, "A Four-Week Oral Toxicity Study in Dogs with Sutan® Technical", (Ira W. Daly, Bio/dynamics, Inc., East Millstone, NJ., Report # T-12650, 16 May 1986). Submitted by Stauffer Chemical Co. The test article is identified as Sutan® Technical (100% purity). 24 Beagle dogs, 2/sex/group received 0, 100, 300, 600, 900, and 1200 mg/kg/day in gelatin capsules for 4 weeks. Control animals received empty gelatin capsules. All dogs at 600, 900, and 1200 mg/kg/day were sacrificed on day 19 because of toxicity and weight loss. Reduced bodyweights were noted for both sexes at 300 mg/kg/day and higher. Elevated alkaline phosphatase values, increased relative liver weights, and perivascular accumulation of lymphoid cells/neutrophils in the liver were recorded at terminal sacrifice for all animals at 100 mg/kg/day and higher. Alterations in hematology and clinical chemistry parameters consistent with liver damage and altered liver functions were noted at dose levels of 100 mg/kg/day and greater. **Supplemental** information. No worksheet. (H. Green and P. Iyer, 11/6/96).

048 065970, "A Four-Week Oral Toxicity Study in Dogs with Sutan® Technical", (Ira W. Daly, Bio/dynamics, Inc., East Millstone, NJ., Report # T-12650, 16 May 1986). Submitted by ICI Americas Inc. Duplicate of 043 062438.

012 023104, "A 16-Week Dietary Feeding Study in Dogs with Sutan® Technical", G. Woodard, Woodard Research Corporation, Herndon, VA. 2/14/67. Report # T-2053, Submitted by R. Potrepka, Stauffer Chemical Company, Farmington CT., 12/14/84. Sutan® Technical was administered in the diet at concentrations of 0, 450, 900 or 1800 ppm to 4 beagle dogs of each sex (controls) and 3 dogs of each sex for the treatment groups such that a dose level of 10, 20 and 40 mg/kg/day was achieved (animals were fed 200 gms/day). Parameters examined included survival, body weight gain, food consumption, clinical chemistry, urinanalysis, hematology, neurological and ophthalmological examinations, blood pressure, electrocardiograms, heart rates, gross necrops, organ weights, organ to body weight ratios, and histopathology. No treatment-related adverse effects were observed. No worksheet. Subchronic study, supplemental information (P. Iyer, 4/21/97).

ONCOGENICITY, RAT

See Combined, Rat.

ONCOGENICITY, MOUSE

064 128431, "Lifetime Oral Study in Mice", (Edwin Goldenthal, International Research and Development Corporation, Mattawan, MI., Report # 153-008, 13 August 1979). The test article identified as Sutan Technical (98% purity) was administered in the diet to 60 Charles River CD-1 mice/sex/group at concentrations of 0 (Purina® Laboratory Chow®, corn oil), 20, 80, and 320 mg/kg/day for 2 years. 10/sex/group were sacrificed at 1 year. During weeks 38 and 39, all mice received untreated basal diet reportedly because test article was unavailable. Increased relative liver weights were recorded at terminal sacrifice for 20, 80, and 320 mg/kg/day females. Increased incidence of nodular hyperplasia of the liver is indicated for low, mid, and high dose males. **Adverse effects are not indicated**. Chronic NOEL = 80 mg/kg/day (liver hyperplasia, organ weight differences). Oncogenicity NOEL = 320 mg/kg/day. **Unacceptable**, upgradeable (clarification of histopathology). (H. Green and P. Iyer, 3/21/97).

063 128429, "Six Week Range Finding Study in Mice", (Edwin I. Goldenthal, Ph.D., International Research

and Development Corporation, Report # T5989, 30 July 1976). The test article is identified as Sutan Technical with 98% purity. 5 Charles River CD-1 mice per sex per group received 40 (was increased to 1280 mg/kg/day for weeks 4-6), 80, 320, or 640 mg/kg/day in the diet for 6 weeks. At 640 mg/kg/day, slight emaciation was noted for 1 male and 1 female. Emaciation, paleness, hypothermia, and altered posture were recorded at 1280 mg/kg/day. One 40/1280 mg/kg/day male died at week six.
(H. Green, 4/18/94, no worksheet).

012, 022837, "Lifetime Oral Study in Mice (Sutan® Technical)", International Research and Development Corporation, Mattawan, MI. August 1979.
Duplicate of 064, 128431.

015, 037014, "Lifetime Oral Study in Mice (2 years)", International Research and Development Corporation, Mattawan, MI. August 1979.
Duplicate of 064, 128431.

016, 037015, Addendum to Lifetime Oral Study in Mice (Sutan® Technical), Test Diet Preparation and Test Diet Analysis. Stauffer Chemical Co. Western Research Center, Richmond, CA. August 1983. No worksheet.

REPRODUCTION, RAT

50, 033, 034, 035, 012 065972, 046815, 046816, 046817, 022834, "A Two-Generation Reproduction Study in Rats with Sutan®", (J.L. Minor, Stauffer Chemical Company, Environmental Health Center, Farmington, CT., Report # T-11940, 18 June 1986). The test article is identified as Sutan Technical with 98.2% purity. 25 CrlCD*(SD)BR rats per sex per group received 0 (Purina Certified Rodent Meal # 5002), 200, 1000, and 4000 ppm in the diet through 2 generations with 2 matings in the first and 3 matings in the second generation. Food consumption and hematocrit values were reduced for parental males and females at 4000 ppm. **No adverse effect is indicated. Parental NOEL = 1000 ppm (7% to 17% bodyweight reduction at 4000 ppm). Reproductive NOEL = 1000 ppm (reduced pup weight gain at 4000 ppm). **Acceptable** (H. Green and P. Iyer 3/24/97).

TERATOLOGY, RAT

031, 012 037030, 022830, "A Teratology Study in CD® Rats with Sutan® Technical", (J.R. Downs, Stauffer Chemical Company, Environmental Health Center, Farmington, CT., Report # T-11713, 22 August 1983). The test article is identified as Sutan Technical with 98.2% purity. 26 to 28 mated Sprague-Dawley female rats per group received 0 (corn oil), 40, 400, or 1000 mg/kg/day by gavage on gestation days 6 through 20. Reduced maternal bodyweights and increased relative liver weights were recorded at 1000 mg/kg/day. **No adverse teratogenic effects are indicated. Maternal NOEL = 400 mg/kg/day (clinical signs, early resorptions, mortality at 1000 mg/kg and decreased body weights at 400 and 1000 mg/kg/day). Developmental NOEL = 400 mg/kg/day (increased litter resorptions, reduced number of litters, and decreased fetal weights at 1000 mg/kg/day). **Acceptable**. (H. Green, and P. Iyer, 3/17/97).

TERATOLOGY, MOUSE

012 022835, "R-1910, Safety Evaluation by Teratological Study in the Mouse", Robert P. Beliles, Ph.D., Woodard Research Corporation, Herndon, VA., Report # T-6263, the cover letter is dated 14 December 1984 and the report is dated 26 April 1967). The test article is identified as R-1910 (butylate) technical with 97.6% purity. 20 or 40 inseminated female mice per group received 0, 4, 8, and 24 mg/kg/day in the diet on gestation days 6 through 18. Half of the dams per group were delivered by C-Section (day 18), the

others were allowed to deliver naturally. **No maternal or fetal effects are indicated**. Maternal and Developmental NOEL = 24 mg/kg/day. NOAEL = 24 mg/kg/day. **Unacceptable** and not upgradeable (dosing level rationale, diet analyses). (J. Remsen, 10/18/85; updated to electronic format, H. Green, 3/8/96).

TERATOLOGY, RABBIT

040, 047 062442, 065969, "A Teratology Study in Rabbits with Sutan® Technical", (S. L. Wilczynski, Stauffer Chemical Company, Farmington, CT 06032, Report # T-12999, 16 September 1987). The test article is identified as Sutan® Technical with 99% purity. 16 mated female New Zealand White rabbits per group received 0 (corn oil), 10, 100, and 500 mg/kg/day by gavage on gestation days 7 through 19. An increased number of skeletally normal fetuses and a reduced number of fetuses with full-sized ribs were recorded at 10 mg/kg/day. Increased relative maternal ovary weights were recorded at 500 mg/kg/day. **Teratogenicity is not indicated. Maternal NOEL = 100 mg/kg/day (reduced body weight with concurrent reduction in food consumption at 500 mg/kg/day). Develpmental NOEL = 500 mg/kg/day. **Acceptable**. (H. Green, and P. Iyer, 3/17/97).

042, 049 062436, 065971, "A Range-Finging Teratology Probe in Rabbits with Sutan® Technical", (J. L. Minor, Stauffer Chemical Company, Farmington, CT 06032, Report # T-12998, 11 September 1987). The test article was identified as Sutan® Technical with 99% purity. 6 mated female New Zealand White rabbits per group received 0 (corn oil), 10, 100, 200, 400, and 800 mg/kg/day by gavage on gestation days 7 through 19. No worksheet (P. Iyer, 3/17/97).

GENE MUTATION

036, 051 046818, 065973, "Mutagenicity Evaluation in Salmonella Typhimurium", (Jenness B. Majeska, M.S., The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT, Report # T-12684, 21 October 1985). The test article is identified as Sutan® Technical with 99% purity. Salmonella typhimurium strains TA-98, TA-100, TA-1535, and TA-1537 were exposed 48 hours at 0 (medium), 0 (DMSO), 0.313, 0.625, 1.250, 2.500, and 5.000 ul/plate in the presence and absence of activation (Aroclor 1254 (500 mg/kg) induced Sprague-Dawley male rat and CD1 male mouse S9 liver fractions) in the reversion assay. **Increased reversion frequency is not indicated. **Acceptable**. (H. Green and P. Iyer, 11/20/96).

051 065974, "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Forward Mutation Assay", (Jenness B. Majeska, The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT., Report # T-12685, 8 August 1986). The test article is identified as Sutan® Technical with 99% purity. Duplicate cultures of 6 x 10^5 L5178Y mouse lymphoma cells/ml were exposed 4 hours in the presence of activation at 0 (medium), 0 (DMSO), 0.0125, 0.0250, 0.0410, 0.0500, 0.0510, 0.0600, 0.0610, 0.0700, 0.0710, 0.0800, 0.0810, 0.1000, and 0.1200 ul/ml and without activation at 0 (medium), 0 (DMSO), 0.0310, 0.0360, 0.0400, 0.0410, 0.0440, 0.0450, 0.0480, 0.0500, 0.0520, 0.0550, 0.0560, 0.0600, and 0.0650 ul/ml. **Increased forward mutation is not indicated. **Acceptable** (H. Green and P. Iyer, 11/25/96).

CHROMOSOME EFFECTS

****062, 051 128428, 065975,** "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test, Cytogenetic Assay", (Jenness B. Majeska, The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Co., Farmington, CT. 06032, Report # T-12686, 30 April 1986). The test article is

identified as Sutan Technical with 99 % purity. 50 mouse L5178Y (TK+/-) lymphoma cells per culture were exposed in duplicate without activation at 0 (medium), 0 (DMSO), 0.010, 0.020, 0.040, or 0.060 ul/ml and with activation at 0 (medium), 0 (DMSO), 0.050, 0.065, 0.080, 0.100, and 0.120 ul/ml. Chromosomal aberrations and sister chromatid exchanges were evaluated in separate assays. **Increased frequency of sister chromatid exchange is indicated in the presence of activation**. **Acceptable**.
(H. Green and P. Iyer, 11/27/96).

DNA DAMAGE

036, 051 046819, 065976, "Morphological Transformation of BALB/3T3 Cells", (Jenness B. Majeska, M.S., The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT., Report # T-12687, 12 November 1985). The test article is identified as Sutan Technical with 99% purity. Mouse BALB/3T3 cells received 3 day exposure without activation at Medium, 0 (DMSO), 0.01, 0.02, 0.04, and 0.06 ul/ml with 15 replicates per dose level in the morphologic transformation assay. **Increased transformation in the absence of activation is not indicated**. **Unacceptable**. No activation. (H. Green and P. Iyer, 3/28/97).

036, 051 046820, 065977, "Effects of Sutan® Technical on Human Fibroblast DNA", (Ronald D. Snyder, Ph.D., The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT., Report # T-12688, 19 December 1985). The test article is identified as Sutan® Technical with 99% purity. Human foreskin fibroblasts were exposed for 1 or 2 hours in the presence and absence of activation (Aroclor 1254 (500 mg/kg) induced male Sprague-Dawley rat liver S9) at 1.68 ul/ml. **Increased DNA damage is not indicated**. **Unacceptable**, upgradeable (dosing rationale, cell survival data and individual values). (H. Green and P. Iyer, 4/4/97).

NEUROTOXICITY

032, 012 037031, 022831, "Acute Delayed Neurotoxicity Study with Technical Sutan in Adult Hens", (Dr. G. L. Sprague, Richmond Toxicology Laboratory, Stauffer Chemical Company, Richmond, CA., Report # T-6801, 1 October 1980). The test article is identified as Sutan Technical with 98.2% purity. 12 or 15 White Leghorn hens per group received 0 (corn oil) or 9317 mg/kg by gavage two times (with a 22 day interval) with protection (20 mg/kg atropine sulfate). **Delayed neurotoxicity is not indicated. Acceptable (H. Green and P. Iyer, 4/18/97).

065 132851, "Butylate: Subchronic Neurotoxicity Study in Rats", (A. Brammer, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P/4423, 2 September 1994). The test article is identified as Sutan (butylate) technical with 95.7% (w/w) purity. 12 Alpk:APfSD rats per sex per group received 0, 250, 1000, and 5000 ppm test article in the diet for 13 weeks. Group mean food consumption was reduced for high-dose males and females (8% to 22% reduction) and for 1000 ppm females (10% to 14%) compared to control values. Systemic NOEL = 250 ppm. Neurotoxicity NOEL and NOAEL = 5000 ppm. **Acceptable (H. Green and P. Iyer, 4/7/97).

****066 134265**, "Butylate: Acute Neurotoxicity Study in Rats", (S. A. Horner, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P/4404, 1 December 1994). The test article is identified as Sutan (butylate) technical with 95.6% (w/w) purity. 10 Alpk:APfSD rats per sex per group received a single test article dose by gavage at 0, 200, 600, and 2000 mg/kg followed by 15 days of observation. Increased signs of urinary incontinence for females at 600 and 2000 mg/kg relative to controls were recorded. Clinical NOEL = 200 mg/kg. Neurotoxicity NOEL and NOAEL = 600 mg/kg (**decrease in brain weight in females and neuronal cell necrosis in males at the high dose**). **Acceptable** (H. Green and P. Iyer, 4/14/97).

OTHER

067 135243, "Thiocarbamates: Comparative In Vivo Percutaneous Absorption Study in the Rat", (R. E. Lythgoe and J. A. Platt, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P/4594, 1/12/95). The test article is identified as butylate emulsifiable concentrate with 95.7% (w/w) purity (unlabelled) and 98.4% purity ([14C]-labelled). 4 males received a 10-hour, shaved, non-abraded, dermal exposure to 14C labelled test material at 0.282 mg per rat. The % of applied butylate absorbed ranged from 3.751% to 4.779%. This is considered **supplemental** information. (H. Green and P. Iyer, 4/11/97).

070 158959 “First Revision to Butylate: Acute Neurotoxicity Study in Rats”, S.A. Horner, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P/4404; Study No: AR5701, 7/14/95. Reassessment of the Acute Neurotoxicity study in rats. Neurotoxicity NOEL and NOAEL = 600 mg/kg (**decrease in brain weight in females and neuronal cell necrosis in males in the pyriform cortex and/or the dentate gyrus at the high dose of 2000 ppm**). Supplemental. No worksheet (P. Iyer, (2/27/98).

071 158960, “First Supplement to Butylate: Subchronic Neurotoxicity Study in Rats", (A. Brammer, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P/4423, Study No: PR970, 7/12/95. Submission of all clinical observational data generated as part of the Functional Observational Battery in weeks 1, 5, 9 and 14 including negative findings. Summary data and individual animal data are provided. Supplemental. No worksheet (P. Iyer, 2/27/98).

072 158961, “Thiocarbamates: Selective Re-examination of Neuropathology”, D.T. Chalmers, S. J. Duffell and S.A. Horner, Zeneca Central Toxicology Laboratory, Cheshire, UK., Report # CTL/P4618; Study No: PR0999, 3/28/95. Report of study undertaken to re-examine selected areas of the rat brain from previously conducted acute neurotoxciity, sub-chronic neurotoxicity and sub-acute inhalation studies. Newly established criteria were used to determine neuronal cell necrosis in specific areas of the brain (dendate gyrus and pyriform cortex). Similar lesions were observed in a number of thiocarbamates namely, cycloate, EPTC, pebulate, vernolate and butylate. A systematic approach to detecting and determining these histopathological lesions is evident. Photomicrographs submitted in this report are from studies on cycloate, EPTC and pebulate. Supplemental, no worksheet (P. Iyer, 2/27/98).

The following volumes and record numbers have been examined.

Volume	Record Numbers
232-012	022830
"	022831
"	022832
"	022833
"	022834
"	022835
"	022836
"	022837
"	023103
"	023104
232-014	022836
"	037013
232-015	037014

232-016	037015
232-017	037016
232-018	037017
232-019	037018
232-020	037019
232-021	037020
232-022	037021
232-023	037022
232-024	037023
232-025	037024
232-026	037025
232-027	037026
232-028	037027
232-029	037028
232-030	037029
232-031	037030
232-032	037031
232-033	046815
232-034	046816
232-035	046817
232-036	046818
"	046819
"	046820
232-040	062442
"	
232-041	062437
232-042	062436
232-046	065968

232-047	065969
232-049	065971
232-050	065972
232-051	065973
"	065974
"	065975
"	065976
"	065977
232-055	073368
"	073369
"	073370
"	085224
232-062	128428
232-064	128431
232-065	132851
232-066	134265
232-067	135243
232-070	158959
232-071	158960
232-072	158961